UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,163	09/09/2004	Nicholas John Newcombe	056291-5180	2793

9629 7590 03/18/2008

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
03/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,163	NEWCOMBE ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20071119 & 20080130*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on November 19, 2007.

Claims 1-11 and 22-25 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The terminal disclaimer filed on January 10, 2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,969,714 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The provisional obviousness-type double patenting rejection over claims of copending Application No. 10/507,162 is withdrawn in view of the amendments. It has been deemed that the claims of each of the application are not overlapping.

The following rejections are maintained:

1. Claims 1-11 and 22-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8-10 and 21-24 of copending Application No. 10/507,169. The reasons provided in the previous office action are incorporated here by reference.

2. Claims 1-11 and 22-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17, 21, 33 and 35 of

copending Application No. 10/507,081. The reasons provided in the previous office action are incorporated here by reference.

It is acknowledged that applicants will address the above rejections when the claims are in condition for allowance. The rejections are maintained as there still issues remaining in this application.

The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, does not reasonably provide enablement for a method for producing a cell cycle inhibitory (anti-cell proliferation) effect; a method for the inhibition of CDK2, CDK4, or CDK6; or a method for treating cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The

determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims 22 and 23 are drawn to 'a method of producing a cell cycle inhibitory (anti-cell-proliferation) effect' and 'a method for the inhibition of CDK2, CDK4 or CDK6' and the specification provides that 'in view of the biological properties, the compounds are suitable for treating wide range of diseases' and therefore, the instant claim reads on the corresponding therapeutic effect of the compounds in patients. The specification at pages 14-15 provides that 'the activity of the compounds may be assessed by *in vitro* procedures provided in WO 02/04429' and the specification provides a range of IC_{50} data for the compounds of the invention, however, there is no actual test procedure or the corresponding data for the compounds of the invention. The instant claims however, are drawn to 'a method of producing a cell cycle inhibitory (anti-cell-proliferation) effect' and 'a method for the inhibition of CDK2, CDK4 or CDK6' and thus, drawn to the corresponding treatment associated with the inhibitory activity. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention. As disclosed in the specification, the diseases and disorders encompassed by the instant claims include various types of anti-cell proliferation diseases, leukaemias, fibroproliferative diseases, cancer, bone diseases, etc. some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that

the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The instant claims 24-25 are drawn to 'a method of treating cancer' and 'a method of treating leukemia, breast cancer, ... and cancer of the vulva'. The instant claims cover all types of cancer, including those that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The specification at pages 14-15 provides that 'the activity of the compounds may be assessed by *in vitro* procedures provided in WO 02/04429' and the specification provides a range of IC_{50} data for the compounds of the invention, however, there is no actual test procedure or the corresponding data for the compounds of the invention. The disorders encompassed by the instant claims include diseases caused by the proliferation of tumor cells, etc. some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific

area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Regarding CDK mechanism, Blain et al. (J. of Biol. Chem.) report that "their specific functions are still poorly understood" (see page 25863, col. 1). Also, LuValle et al. (Frontiers in Bioscience) express that "detailed analyses of these pathways are necessary for a complete understanding of chondrocyte proliferation and differentiation" (see page 495, section 4). This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

Claims 24-25 specifically include 'a method for treating several types of cancer' - no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see page 1004). A 'disease caused by proliferation of tumor cell' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. Different types of cancers affect different organs

and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or disorders caused by kinases generally.

Further, there is no established single antiproliferative therapeutic agent for all these types of diseases, which are characterized by the proliferation of tumor cells. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states, that "Treatment programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear. Similarly, Myelodysplastic syndrome (MDS) is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms and its incidence is unknown and further, there is no established treatment. Several growth factors and their receptors have been associated with glioma and the treatment depends on the pathology and location and is often multimodal.

Further, there is no disclosure regarding how the patient in need of such specific CDK

inhibiting activity is identified and further, how all types of cancers. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in producing cell cycle inhibitory effect; a method for the inhibition of CDK2, CDK4 or CDK6; etc.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat patients suffering from all types of diverse diseases mediated by kinases. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that 'pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles' see page 585, col. 2, lines 33-36.

3) The predictability or lack thereof in the art: Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, 'the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved'. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one of ordinary skill in the art to use the compounds in the treatment of all of the diseases or disease symptoms within the scope of the claims. The specification provides a source for test procedures for the measurement of CDK kinase inhibitory activity of the compounds and a possible IC_{50} range for the compounds of the invention. However, there is disclosure regarding how this data correlates to the inhibition of all the types of CDKs and/or to the treatment of all diseases mediated by CDKs.

6) The breadth of the claims: The instant claims embrace inhibiting CDK2, CDK4 or CDK6 activity in general and treating diseases related to those kinases in general.
7) The quantity of experimentation needed would be an undue burden, because it is not known what type of 'diseases' are referred to in the claims. Further, it would be an undue burden on one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the medical conditions or illnesses included in the instant claims.

It is inconceivable as to how the claimed compounds can treat the large list of diseases associated with the instantly claimed activity of CDK inhibition. Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific kinase inhibiting activity is identified and further, how all types of the diseases having diverse mechanisms are treated. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity, see Blain et al. and LuValle et al. referred above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Receipt is acknowledged of the Information Disclosure Statements filed on November 19, 2007 and January 30, 2008 and copies are enclosed herewith.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

March 20, 2008